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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,401	02/27/2007	Seth Hallstrom	16785.10	8352

22913 7590 03/28/2012

Workman Nydegger
1000 Eagle Gate Tower
60 East South Temple
Salt Lake City, UT 84111

EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
03/28/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,401	HALLSTROM ET AL.	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/25/12 & 9/26/11*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1, 2, 7 and 14* is/are pending in the application.

5a) Of the above claim(s) *none* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,2,7 and 14* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 2, 7 and 14 are under examination. The applicants' response (filed 1/25/12) to the Office action mailed 9/26/11 does not contain claim amendment.

Maintained-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7 and 14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Schlag et al. (US Pat. No. 6358918 B1) or Hallstrom et al. (2002) *Circulation*, 105, 3032-3038) in view of Demopoulos et al. (US 2002/0136763 A1) and/or Lipton S. A. (UA Pat. No. 6525017 B1).

Schlag et al. teach a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one

(*plurality*) thiol-group containing protein (claim 16); wherein at least 95% or 90% of the thiol groups of said protein are nitrosated, i.e., S-nitrosated protein (claims 19 and 20), and wherein said "at least one thiol-group containing protein" that has been nitrosated is S-nitroso-albumin (claim 21), as applied to claim 1.

Schlag et al. teach that, in their invention the "mixtures" of nitrosated proteins or proteins capable of being nitrosated (i.e., proteins that have not been nitrosated and still have free thiol groups) is particularly preferred (col.2, lines 58-60). This suggests that, in addition to the nitrosated protein, e.g., "S-nitroso-albumin" (S-NO-albumin), any other protein(s)/peptide(s) (in agreement with the above-discussed "*plurality*") which potentially could include GSH) that contains free thiol groups can be combined with the S-NO-albumin.

Schlag et al. further teach that the thiol-group containing protein has N-nitrosation, O-nitrosation and/or C-nitrosation level of less than 10% (patent claim 24), and S-nitrosation level of at least 95% or 90% (patent claims 19 and 20), as applied to instant claims 2, 7 and 14 herein.

Hallstrom et al. also teach the use of S-nitrosated human serum albumin (S-NO-HSA) to treat ischemic condition, i.e., ischemia/reperfusion injury of skeletal muscle in a rabbit (see the entire document).

Yet, neither Schlag et al. nor Hallstrom et al. expressly teach combination of the S-NO-albumin with the reduced glutathione (GSH) for treating ischemia.

However, Demopoulos et al. teach glutathione can be used in combination with other therapies (i.e., suggesting the combination with other therapeutic agents or proteins) for treating free radical associated disorders, e.g., ischemic event (see [0115], lines 1-3 and 6).

Alternatively, Lipton also discloses a method of treating patients with nervous system

ischemia by administering to said patient a pharmaceutical composition comprising reduced glutathione GSH (see patent claims 3 and 4).

With the teachings of the above references in hand, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine S-nitroso albumin (S-NO-HSA) and GSH for treating the ischemia. This is because Schlag et al. teach the benefits of treating ischemia using S-NO-albumin, and that it is particularly preferred to use "mixtures" (combination) of nitrosated proteins for example "S-NO-albumin" with "any other proteins/peptides" containing free thiol groups wherein said any other proteins/peptides could potentially include GSH. Hallstrom et al. also teach that GSH has a capability of scavenging superoxide (O_2^-) that causes the tissue ischemic damage. Because of this well-known teaching in the prior art it is also arguable that one of ordinary skill in the art would have chosen GSH as one of said "any other proteins/peptides" in the "mixtures" taught by Schlag et al.

Further, Demopoulos et al. have also taught a feasibility of combining glutathione with other "therapeutic protein(s)/peptide(s)" for treating therapies (i.e., suggesting free radical associated disorders, e.g., ischemia (see above). Here, glutathione is considered to be one of said "therapeutic protein(s)/peptide(s)" (see [0001], Domopoulos et al.). Upon reading the above references, one of ordinary skill in the art would have readily realized the benefits of including the GSH along with the nitrosated albumin in the treatment of ischemia, not only due to the capability of GSH in scavenging superoxide that causes tissue ischemic damage as taught by Hallstrom, but also, due to the fact that GSH has been demonstrated to be therapeutically active in treating ischemia (see the Lipton's US patent and Demopoulos's teaching above).

Based on the above discussed motivations, one of ordinary skill in the art would have

readily added GSH to the formulation of S-NO-albumin, e.g., S-NO-HAS, with GSH, and would have used said formulation to treat ischemia with reasonable expectation of success. Therefore a combination of the teachings of either Schlag/Hallstrom and Lipton or Schlag/Hallstrom and Demopoulous renders the claimed method *prima facie* obvious.

The applicants' response to the 103(a) rejection above

From page 13 to 14, the response filed 1/25/12 submits that office fails to consider claimed invention as a whole and make impermissible use of hindsight, and that there is no apparent connection between the disparate/ piecemeal teachings of the references as there is no teaching/suggestion for co- administration of S-introso albumin (S-NO-albumin) and reduced glutathione (GSH) The response asserts that the only conceivable motivation in the record is Applicants' own disclosure.

The response asserts that Schlag and Hallstrom do not teach combination of the S-NO-albumin with GSH, and, Lipton teaches only administration of GSH alone or in combination with other therapeutic agents for treating a free radical-associated disorders, whereas Demopoulos et al. cite a laundry list of other therapeutic agents that glutathione may be used in combined with other therapeutic agents (see also p.10, 1st paragraph), and thus, Demopoulos in no way suggests said "combination" (page 5, last paragraph to page 6, 2nd paragraph, the response).

The response argues that the prior art of the record is silent as to the synergistic and dose-dependent benefits that may be achieved by co-administration of S-nitroso albumin and GSH (page 6, 4th paragraph), and that selecting a pharmaceutical for treating ischemia is challenged by a large number of potential sources thereof, i.e., the combination of S-NO-albumin with GSH regard impermissible hindsight (page 6, last paragraph to page 7, 2nd paragraph).

From pages 7-11, the response argues that 103 references fail to teach/suggest every element of instant claims, and that combinations of Schlag, HallstrOm, Demopoulos, and Lipton fail to teach/suggest co-administration of GSH and S-NO-albumin. The response argues glutathione toxicity or side effect that requires undue experimentation for therapeutic use of GSH (p.9, 2nd paragraph, lines 12-21). The response Schlag teaches away from nitrosated preparation of instant claims due to Schlag advocating their nitrosated preparation that delay release of NO (page 11, paragraphs 1-3).

In addition, from pages 11-13, the response argues the unexpected results via discussion of Examples 1-3, and infer that the unexpected results show objective evidence of non-

obviousness of the claimed method (p.6, last paragraph). Further, at page 13, paragraphs 3-4, the response discussed page 6 of the Office action mailed 9/26/11 and argues that the Office does not provide factual indicia for rebutting co-administration of S-NO-albumin and GSH provides a synergistic effect that is unexpected.

Thus, the response requests withdrawal of the rejection.

The applicants' arguments are not persuasive because of the reasons set forth in the above new 103(a) rejection, and the reasons below.

Schlag et al. have taught a method of treating an ischemia (cerebral ischemia) comprising administering to a patient in need thereof a pharmaceutical composition comprising at least one (*plurality*) thiol-group containing protein(s), e.g., S-NO-albumin; the open-ended language "comprising" and "at least (*plurality*) thiol-group containing protein(s)," clearly suggest that, except the S-NO-albumin, otherwise thiol-group containing proteins/peptides (GSH is a potential candidate, see col.2, line 62) can be included in said "pharmaceutical composition"

Although Schlag et al. do not expressly teach use of the S-NO-albumin combined with GSH for treating ischemia, Demopoulos et al. have taught that **GSH** can be used in combination with other therapies to treat an ischemic disorder. Schlag et al. have taught that the "mixtures" of nitrosated proteins with any thiol containing peptides/proteins (not been nitrosated) is particularly preferred (see col.2, lines 58-60) which potentially include **GSH** (see col.2, line 62). Lipton also discloses use of a pharmaceutical composition comprising **GSH** to treat a disorder associated with ischemia.

Additionally, Hallstrom et al. also teach the use of the S-NO-HAS (human serum albumin) to treat ischemic condition, and that Hallstrom et al. also teach that **GSH** has the capability of scavenging superoxide (O_2^-) that causes the tissue ischemic damage.

Further, motivation of the combination of using GSH with S-NO-albumin arises from the reference teachings regarding not only the capability of GSH in scavenging superoxide that causes tissue ischemic damage as taught by Hallstrom, but also, the fact that GSH has been demonstrated to be therapeutically active in treating ischemia (see the Lipton's US patent and Demopoulos's teaching above).

Therefore, with the teachings of combination use of S-NO-albumin (or S-NO-HAS) with GSH in the above references in hand, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine S-nitroso albumin (S-NO-HSA) and GSH for treating the ischemia, and therefore, the combination of the references teach the claimed method as a whole, i.e., the combination use of GSH with S-NO-albumin for treating ischemia. The applicants asserted "make impermissible use of hindsight" is totally unpersuasive.

At [0515], Demopoulos et al. disclose feasible combination of GSH with other therapeutics for treating an ischemic condition wherein the "therapeutics" for treating the ischemic condition has been suggested by Schlag et al. (S-NO-albumin is in the "mixture" which contains any non-nitrosated peptides which might include GSH, see above corresponding discussion), by Hallstrom et al. (**GSH** is capable of scavenging superoxide (O_2^-) which essentially cause the tissue ischemic damage), and by Lipton (in patent claims 3-4, use of a pharmaceutical composition comprising GSH to treat a disorder associated with ischemia. Thus, one of ordinary skill in the art would have readily known that said other therapeutic protein is S-NO-albumin, because, like GSH, in the same line, the ability of S-NO-albumin to treat ischemia has been shown by Domopoulo et al. and/or Lipton. This would establish nexus between treating ischemia using -NO-albumin and using GSH. The applicants' argument "selecting a pharmaceutical for treating ischemia is challenged by a large number of potential sources" is thus not at issue here.

Also, in view of the above combined teachings of the references, a synergistic effect of GSH and the S-NO-albumin for treating ischemia (when compared to treatment with GSH alone or with S-NO-albumin alone) would be expected by one of ordinary skill in the art. It is of note that there is no the "synergistic effect" recited in the instant pending claims.

As far as argument that Schlag teaches away from instant claims due to Schlag's nitrosated preparation delaying release of NO is concerned, the S-NO-albumin (i.e., S-NO-HSA) is identical to instant "S-nitroso albumin" disclosed in claim 1. Do applicants argue against their own invention? It appears that this concern is not at issue.

The instant Example 1- 3 show a drop in blood pressure, an increase in NO release and a drop in platelet aggregation, respectively, when S-NO-albumin and GSH is administered. However, none of these examples provide any factual evidence as to why such events are unexpected or beneficial. Even otherwise, in view of the combined teachings of the above references such events would be inherent to the method and expected by one of ordinary skill in the art. Thus, Examples 1-3 are not considered to have provided the convincing unexpected results to sufficiently establish the asserted non-obviousness.

Neither the "synergistic effect" is recited in the pending claims, nor the "synergistic effect" per se alone can be used alone as an "unexpected result" to overcome the 103 rejection above. The discussion of page 6 of the Office action mailed 9/26/11 in this regard is appropriate. The combination of the 103 references' teachings has established a prima facie case of obviousness, and therefore, the 103(a) rejection is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Samuel Wei Liu/
Patent Examiner, Art Unit 1656
/ANAND U DESAI/
Primary Examiner, Art Unit 1656
March 21, 2012